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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,625	11/03/2003	Ralph M. Ellison	CP380E	3399

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EXAMINER	
PAK, JOHN D	

ART UNIT	PAPER NUMBER
1616	

DATE MAILED: 05/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/698,625	ELLISON ET AL.	
	Examiner	Art Unit	
	JOHN PAK	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-46* is/are pending in the application.

4a) Of the above claim(s) *40,41 and 46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-39 and 42-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *5/04, 10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 24-46 are now pending in this application.

Applicant's election with traverse of the invention of Group I in the reply filed on 2/23/2006 is acknowledged.

Applicant traverses the restriction requirement because "a search and examination of the subject matter of the entirety of the pending claims can be conducted without a serious burden."

Applicant argues that since the Patent Office classifies the subject matter of Groups I to IV in the same class and subclass, this is evidence of "a recognition in the art of a single subject of inventive effort." This is found to be most unpersuasive.

First, applicant's statement is inconsistent with applicant's own prior actions. Applicant has claimed the following in four separately filed patent applications:

Application No.	**Claimed subject matter**
10/640,399	Treatment of multiple myeloma with arsenic
10/649,944	Treatment of lymphoma with arsenic
10/649,776	Treatment of melanoma with arsenic
10/640,403	Treatment of myeloid dysplastic syndrome with arsenic

If indeed there were such "recognition in the art of a single subject of inventive effort" for treatment of all cancer types with arsenic, applicant's separate filing of four different

applications directed to four different types of cancers or pre-cancerous conditions is direct contrary evidence against applicant's arguments here.

Second, the U.S. Patent Classification system is not always indicative of the divergent searches and complex technology-specific considerations that would be required. This is particularly the case in complex technologies where the classification system has not kept up with the developments in the art. For example, applicant argued during the prosecution of 10/649,776 that even a prior art reference that explicitly discloses "body surface tumors" and "skin cancer" is distinguishable over a claim directed to melanoma because there are many different types of skin cancers, such as basal cell carcinoma, squamous cell carcinoma, cutaneous T-cell lymphomas, Kaposi's sarcoma (reply filed on 3/7/2006). Applicant argued that different approaches are taken towards treating different types of skin cancer and the prior art disclosure of "body surface tumors" and "skin cancer" fails to provide reasonable expectation of success for treating melanoma. Clearly, applicant's arguments there are squarely in contradiction of applicant's argument in this application. The same inventors clearly recognized a separate inventive effort even among different types of skin cancers. For applicant (same applicant, same inventors) to argue that there is not a separate inventive effort here is difficult to accept or understand, when the types of cancers covered here are far more divergent than mere skin cancer types.

Applicant also argues that the search and examination of the four invention groups would not impose a serious burden on the Examiner. The Examiner cannot agree. As shown above, the examination of this application may turn on the preciseness of prior art teachings and technology-specific issues, and the burden represented by having to separately search AND separately consider the various different types of cancers to be treated vis-a-vis the prior art would place an undue burden on the Examiner. Undue burden is a relative and balanced concept since if the Examiner were given several weeks of time to search and examine this application, the burden would decrease. Applicant should keep in mind that this Examiner is given less than 14 hours to complete this case, from start to finish (allowance, abandonment or Examiner's Answer). Undue burden is also in plain view just from applicant's several information disclosure statements: 8 pages worth of prior art listing were submitted. With so much relevant prior art and so many different types of cancers to consider, the specifics of this application support the Examiner's previous determination of undue burden.

Applicant's traversal of the outstanding restriction requirement is therefore found unpersuasive and the restriction requirement of record is thereby made FINAL.

Examination of this application shall be limited to the elected subject matter. Claims 24-39 and 42-45 will presently be examined *to the extent* that they read on the

elected subject matter. Claims 40-41 and 46 are withdrawn from further consideration as being directed to non-elected subject matter.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 24 is rejected under 35 U.S.C. 102(b) as being anticipated by Stephens et al.[1]

Stephens et al. explicitly disclose treating chronic myelogenous leukemia by combining potassium arsenite (Fowler's solution) with "roentgen treatments," i.e. radiation treatment. See page 1488, second paragraph. Case 1 discloses starting Fowler's solution treatment two weeks after the last radiation treatment. The patient had "extensive myeloid infiltrations in the spleen and liver (page 1490, third full paragraph). Case 3 discloses radiation treatment before and after Fowler's solution (page 1492, fifth and sixth full paragraphs). Case 4 also discloses radiation treatment before and after Fowler's solution (pages 1492 and 1494).

Claim 24 is thereby anticipated.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 24-39 and 42-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Zhang, Kwong et al. and Chen, in view of Stephens et al. and Medline abstract 83131994.

Zhang (US 6,720,011) discloses treating various cancers with arsenic trioxide. See column 1, lines 4-6, 33-35 and 41-43. Treatment of leukemia is set forth (claims 1-4). Treatment of acute promyelocytic leukemia (AML) is exemplified (columns 2-3). Intravenous composition containing 1-10 g arsenic trioxide, sodium chloride and water is disclosed (column 1, lines 41-54). "[S]trong abruptive effect on the membranes of cancer cells" is disclosed, as well as inhibition of DNA/RNA synthesis (column 1, lines 58-61). Effective daily dose for an adult is disclosed as 10 ml of the composition containing 10 g/l arsenic trioxide added to 500 ml of 10% glucose solution is disclosed. This calculates to about 67 mg/day. Appropriate dose is to be "decreased accordingly for children" (column 2, lines 9-16).

Kwong et al.[2] disclose the use of arsenic trioxide for treating chronic myeloid leukemia (CML) and acute myeloid leukemia (page 3487). 10 mg/day of arsenic trioxide via IV resulted in complete morphologie remission in acute promyelocytic

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[1] Stephens, D.J. et al., "The therapeutic effect of solution of potassium arsenite in chronic myelogenous leukemia," Ann. Intern. Assoc., Vol. 9, pages 1488-1502 (1936), cited by applicant in the IDS of 5/19/04.
[2] Kwong et al., Blood, Vol. 89, pages 3487-88 (May 1997), cited by applicant in the IDS of 5/19/04.

leukemia (APL) patients (left column of page 3487, first paragraph). Arsenic trioxide is disclosed as "effective for leukemias of different morphologie types" and such activity is disclosed to be related to intrinsic toxicity of arsenic to marrow cells (page 3487, right column). Arsenic trioxide is also disclosed to induce apoptosis and differentiation of APL cells (page 3487, right column, last sentence).

Chen et al.[3] disclose arsenic trioxide to be effective and relatively safe in the treatment of APL (abstract, pages 3351-52). Arsenic trioxide as a dose-dependent dual effect on APL cells, wherein apoptosis occurs at higher concentrations and differentiation occurs at lower concentrations (page 3351, left column, last full paragraph). Partial differentiation of APL cells followed by cell death is also disclosed (id.). Lack of cross-resistance is disclosed between arsenic trioxide and all-trans retinoid acid, which is another antileukemic chemotherapeutic agent (page 3345, left column, second paragraph).

Stephens et al. disclose "[f]or many years roentgen therapy has been the most satisfactory method of treatment of the chronic leukemias" (page 1488, lines 1-2). Stephens et al. disclose treating chronic myelogenous leukemia by combining potassium arsenite (Fowler's solution) with "roentgen treatments," i.e. radiation treatment. See page 1488, second paragraph. Case 1 discloses starting Fowler's solution treatment two weeks after the last radiation treatment. The patient had

[3] Chen et al., Blood, Vol. 89(9), pages 3345-53, cited by applicant in the IDS of 5/19/04.

"extensive myeloid infiltrations in the spleen and liver (page 1490, third full paragraph). Case 3 discloses radiation treatment before and after Fowler's solution (page 1492, fifth and sixth full paragraphs). Case 4 also discloses radiation treatment before and after Fowler's solution (pages 1492 and 1494).

Medline abstract 83131994 discloses radiation treatment of AML patient to prepare for bone marrow transplantation.

The difference between the claimed invention and the cited references is that the references do not explicitly disclose a combination of arsenic trioxide with radiation to treat leukemia. The cited references also do not explicitly disclose a further combination of at least one more therapeutic agent such as all-trans retinoic acid. However, such combination therapies would have been fairly suggested from the conventional practice in the cancer treatment field to combine the actions and benefits of several therapies to attack the cancer cells from a variety of mechanisms. One having ordinary skill in the art would have been motivated to combine radiation treatment, which is known to be effective for various leukemia types, with arsenic trioxide with the expectation that both therapies would benefit the patient in treating leukemia such as AML (APL is a subtype of AML) and CML. The ordinary skilled artisan would have been further motivated to incorporate an additional therapeutic agents such as all-trans retinoic acid because doing so would attack the leukemia cells from many different approaches and mechanisms for ultimate benefit of the patient.

Parenteral administration would have been an obvious delivery route for a cancer drug and applicant's dose is disclosed by Zhang and Kwong et al. Motivation to treat metastasized cancer would have been found from the efficacy of these combination treatments against various anti-cancer mechanisms. Timing of radiation treatment would have been within the skill of the ordinary skilled artisan, who would have been motivated to use the radiation treatment before, after or concurrently with arsenic trioxide depending on patient condition and the severity of leukemia.

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention and the claimed invention as a whole have been fairly disclosed or suggested by the teachings of the cited references.

Claims 24-39 and 42-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Zhang, Kwong et al. and Chen, in view of Stephens et al. and Witte et al. (US 4,599,305).

Teachings of all references except for Witte et al. were discussed above, and the discussion there is incorporated herein by reference.

Witte et al. establish that various treatments are known for leukemia treatment, wherein acute leukemia "requires immediate treatment utilizing the full range of therapeutic measures available," such as radiation therapy and chemotherapy (column

1, lines 32-45). Radiation is used to treat both chronic lymphoid leukemia and acute leukemias (id.).

The difference between the claimed invention and the cited references is that the references do not explicitly disclose a combination of arsenic trioxide with radiation to treat leukemia. The cited references also do not explicitly disclose a further combination of at least one more therapeutic agent such as all-trans retinoic acid. However, such combination therapies would have been fairly suggested from the conventional practice in the cancer treatment field to combine the actions and benefits of several therapies to attack the cancer cells from a variety of mechanisms (see e.g., Witte et al.). One having ordinary skill in the art would have been motivated to combine radiation treatment, which is known to be effective for various leukemia types, with arsenic trioxide with the expectation that both therapies would benefit the patient in treating leukemia such as AML (APL is a subtype of AML) and CML. The ordinary skilled artisan would have been further motivated to incorporate an additional therapeutic agents such as all-trans retinoic acid because doing so would attack the leukemia cells from many different approaches and mechanisms for the ultimate benefit of the patient. Parenteral administration would have been an obvious delivery route for a cancer drug and applicant's dose is disclosed by Zhang and Kwong et al. Motivation to treat metastasized cancer would have been found from the efficacy of these combination treatments against various anti-cancer mechanisms. Timing of radiation

treatment would have been within the skill of the ordinary skilled artisan, who would have been motivated to use the radiation treatment before, after or concurrently with arsenic trioxide depending on patient condition and the severity of leukemia.

Therefore, the claimed invention, as a whole, would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, because every element of the invention and the claimed invention as a whole have been fairly disclosed or suggested by the teachings of the cited references.

Medline abstract 77108084 is noted for the record as treating brain cancer with an arsenic substance, radiation and another therapeutic agent. This reference was not applied against the elected invention because it does not disclose treating leukemia.

Applicant is requested to update the continuation application information on page 1 of the specification. Applicant is advised that claim 44 contains a typographical error, "after to the arsenic trioxide."

Applicant is further advised that numerous references cited on PTO-1449 were crossed out because they were listed more than once, they were relisted as published patent documents, or they were foreign language documents that did not meet the IDS requirements for proper consideration. A search report cannot be used to indicate relevance when it is not a *counterpart* application.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to JOHN PAK whose telephone number is **(571)272-0620.** The Examiner can normally be reached on Monday to Friday from 8 AM to 4:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's SPE, Johann Richter, can be reached on **(571)272-0646**.

The fax phone number for the organization where this application or proceeding is assigned is **(571)273-8300**. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-1600. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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